## LISTING OF THE CLAIMS

1. (Currently amended) A ~~computer implemented~~ method of identifying one or more ligand conformations that bind to a protein ~~for modeling ligand protein binding interactions~~, the method comprising ~~the steps of~~:

~~providing~~ obtaining structural information ~~describing the structure of a~~ for the protein and for ~~each ligand in a set of~~ one or more ligands;

~~using the structural information for the protein to identify a~~ identifying at least one binding region of the protein;

applying a coarse-grained docking algorithm to identify ~~identifying~~ a plurality of ~~preferred~~ binding conformations for ~~each ligand in the set of~~ the one or more ligands in the binding region;~~, the preferred binding conformations being determined by generating a set of configurations for each ligand by applying a coarse grained docking algorithm and ranking initial~~

selecting best conformations from the binding conformations for the one or more ~~each ligand in the set of~~ ligands ~~at the binding region using energy scoring~~;

optimizing the best conformations using molecular mechanics;

~~preferred binding conformations~~ using annealing molecular dynamics including solvation effects to further optimize a subset of the best conformations~~, the annealing molecular dynamics including solvation effects~~;

minimizing a preferred set of conformations from the subset of the best conformations;

calculating a binding energy for each ~~ligand in~~ conformation of the preferred set of ~~ligands~~ conformations; ~~in the corresponding optimized preferred binding conformations; and~~

ranking the conformations of the preferred set of conformations based on the calculated binding energies;

selecting for each of the one or more ligands ~~ligand in the set of ligands~~ the conformation of the preferred set of conformations having the lowest calculated binding energy ~~in the optimized preferred binding conformations,~~; and

outputting ~~the selected calculated binding energies as the predicted binding energies for the predicted binding conformations of the set of ligands,~~ a data file comprising a list of selected ligand-protein conformations having the lowest calculated binding energy, and their respective binding energies;

wherein the method ~~steps are~~ is performed by a programmable processor executing a program of instructions.

2. (Currently amended) The method of claim 1, wherein the binding region is a known binding region ~~defined by the structural information~~.

3. (Canceled)

4. (Currently amended) The method of claim [[3,]] 1, wherein ~~using the structural information to identify a~~ the identifying at least one binding region of the protein comprises:

mapping [[the]] empty volumes available for ligand binding in the protein to identify one or more potential binding areas ~~regions~~;

generating initial conformations for one or more ligands known to bind the protein using a coarse-grained docking algorithm in each of the one or more potential binding areas; ~~regions and~~

calculating a value of a scoring ~~an energy~~ function for the initial conformations;

selecting from the initial conformations for each of the known ligands a ~~plurality~~ set of best conformations in each of the potential binding regions based at least in part on the ~~preliminary energy scores~~ value of the scoring function; [[and]]

optimizing the conformations in the set of best conformations using molecular mechanics, thereby creating a set of optimized conformations each of which has a corresponding energy score; and

applying spatial clustering to a selection of the optimized conformations having the lowest energies, thereby identifying ~~the probable~~ at least one binding ~~site~~ region ~~based on a spatial location of the best conformations~~.

5. (Canceled)

6. (Currently Amended) The method of claim 4, wherein the selecting is further ~~comprising~~ based on ~~before scoring the energy function for each of the best conformations,~~ ~~calculating for each of the best conformations~~ a calculated percentage of the ligand surface area buried within the protein for the conformation~~, wherein the energy function is scored only for a subset of the best conformations, wherein each of the best conformations in the subset has a calculated percentage of the ligand surface area buried within the protein~~ which exceeds a predetermined threshold.

7. (Canceled)

8. (Canceled)

9. (Currently Amended) The method of claim 1, wherein the annealing molecular dynamics ~~includes~~ uses a full atom force field.

10. (Previously Presented) The method of claim 1, wherein the solvation effects include a continuum description of solvation.

11. (Previously Presented) The method of claim 1, wherein the solvation effects include a surface-area based solvation model.

12. (Currently Amended) The method of claim 1, wherein calculating a binding energy for each ~~ligand in~~ conformation of the preferred set of ~~ligands~~ conformations includes ~~taking the difference in~~ subtracting a free energy of the ~~ligand energy~~ conformation in the protein from a free energy of the conformation [[and]] in solution.

13. (Currently Amended) The method of claim 1, wherein the binding energy for a conformation of the preferred set of conformations is calculated ~~for a ligand~~ according to a scoring function that comprises ~~comprising~~ subtracting the free energy of the ~~ligand~~ conformation in water from the energy of the ~~ligand~~ conformation in the protein.

14. (Currently Amended) The method of claim 1, wherein the binding energy for a conformation of the preferred set of conformations is calculated ~~for a ligand~~ according to a scoring function that comprises ~~comprising~~ subtracting a sum of the free energy of the protein and [[the]] a free energy of the ~~ligand~~ conformation from [[the]] a free energy of the ~~ligand~~ conformation in the protein.

15. (Canceled)

16. (Previously Presented) The method of claim 1, wherein the protein is a globular protein or a transmembrane protein.

17-30. (Canceled)

31. (Currently amended) A computer program product ~~on a computer readable medium~~ for identifying one or more ligand conformations that bind to a protein ~~modeling ligand-protein binding interactions~~, the computer program product comprising instructions operable to cause a programmable processor to:

~~provide~~ obtain structural information ~~describing the structure of a~~ for the protein and for ~~each ligand in a set of~~ one or more ligands;

~~use the structural information for the protein to identify a~~ identify at least one binding region of the protein;

apply a coarse-grained docking algorithm to identify ~~identify~~ a plurality of ~~preferred~~ binding conformations for ~~each ligand in the set of~~ the one or more ligands in the binding region~~; the preferred binding conformations being determined by generating a set of configurations for each ligand by applying a coarse-grained docking algorithm and ranking initial~~

select best conformations from the binding conformations for the one or more ~~each ligand in the set of~~ ligands ~~at the binding region using energy scoring~~;

optimize the best conformations using molecular mechanics;

~~preferred binding conformations~~ use annealing molecular dynamics including solvation effects to further optimize a subset of the best conformations~~, the annealing molecular dynamics including solvation effects~~;

minimize a preferred set of conformations from the subset of the best conformations;

calculate a binding energy for each ~~ligand in~~ conformation of the preferred set of ~~ligands~~ conformations; ~~in the corresponding optimized preferred binding conformations; and~~

rank the conformations of the preferred set of conformations based on the calculated binding energies;

select for each of the one or more ligands ~~ligand in the set of ligands~~ the conformation of the preferred set of conformations having the lowest calculated binding energy i~~n the optimized preferred binding conformations,~~; and

output ~~the selected calculated binding energies as the predicted binding energies for the predicted binding conformations of the set of ligands.~~ a data file comprising a list of selected ligand-protein conformations having the lowest calculated binding energy, and their respective binding energies,

wherein the computer program product is tangibly embodied in a machine-readable storage device for execution by a programmable processor.

32-35. (Canceled)

36. (Currently Amended) The computer program product of claim 31, wherein the instructions to ~~use the structural information to~~ identify at least one binding region of the protein comprise instructions to:

map [[the]] empty volumes available for ligand binding in the protein to identify one or more potential binding areas ~~regions~~;

generate the initial conformations for one or more ligands known to bind the protein using docking techniques in each of the one or more potential binding areas; ~~regions and~~

calculate a value of a scoring ~~an energy~~ function for the initial conformations;

select from the initial conformations for each of the known ligands a ~~plurality~~ set of best conformations in each of the potential binding regions based at least in part on the ~~preliminary energy scores~~ value of the scoring function; [[and]]

optimize the conformations in the set of best conformations using molecular mechanics, thereby creating a set of optimized conformations each of which has a corresponding energy score; and

apply spatial clustering to a selection of the optimized conformations having the lowest energies, thereby ~~identify the probable~~ identifying at least one binding region ~~site based on a spatial location of the best conformations~~.

37. (Currently Amended) The computer program product of claim 31, wherein the annealing molecular dynamics ~~includes~~ uses a full atom force field.

38. (Previously Presented) The computer program product of claim 31, wherein the solvation effects include a continuum description of solvation.

39. (Previously Presented) The computer program product of claim 31, wherein the solvation effects include a surface-area based solvation model.

40. (Currently Amended) The computer program product of claim 31, wherein the instructions to calculate a binding energy for ~~ligand in~~ each conformation of the preferred set of ligands include ~~taking the difference in~~ subtracting a free energy of the ~~ligand energy~~ conformation in the protein from a free energy of the conformation [[and]] in solution.

41. (Currently amended) The computer program product of claim 31, wherein the binding energy for a conformation of the preferred set of conformations is calculated ~~for a ligand~~ according to a scoring function that comprises ~~comprising~~ subtracting the free energy of the ~~ligand~~ conformation in water from the energy of the ~~ligand~~ conformation in the protein.

42. (Currently amended) The computer program product of claim 31, wherein the binding energy for a conformation of the preferred set of conformations is calculated ~~for a ligand~~ according to a scoring function that comprises ~~comprising~~ subtracting a sum of the free energy of the protein and [[the]] a free energy of the ~~ligand~~ conformation from [[the]] a free energy of the ~~ligand~~ conformation in the protein.

43-44. (Canceled)

45. (Currently amended) The computer program product of claim 31, wherein instructions to apply a coarse-grained docking algorithm to identify a plurality of binding conformations and select best conformations ~~generating and ranking initial conformations includes~~ include instructions for: determining a percentage of the ligand surface area buried within the protein for each of the ~~initial~~ binding conformations; and determining energy scores ~~only~~ for a ~~subset~~ portion of the ~~preferred~~ best conformations, wherein each of the ~~preferred~~ best conformations in the ~~subset~~ portion has a calculated percentage of the ligand surface area buried within the protein which exceeds a predetermined threshold.

46. (Currently amended) ~~A computer implemented~~ The method ~~for modeling ligand-protein binding interactions~~ of claim 1, wherein the calculating a binding energy for each conformation of the preferred set of conformations further comprises ~~comprising the steps of~~:

~~providing structural information describing the structure of a protein and each ligand in a set of one or more ligands;~~

~~using the structural information for the protein to identify a binding region of the protein;~~

~~identifying a plurality of preferred binding conformations for each ligand in the set of ligands in the binding region, the preferred binding conformations~~

~~being determined by generating a set of configurations for each ligand by applying a coarse-grained docking algorithm and ranking initial conformations for each ligand in the set of~~ ligands ~~at the binding region using energy scoring~~;

~~optimizing the preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects~~;

~~calculating a binding energy for each ligand in the set of ligands in the corresponding optimized preferred binding conformations, the binding energy being calculated according to~~

calculating a scoring function selected from the group consisting of:

(i) subtracting [[the]] a free energy of the ~~ligand~~ conformation in water from [[the]] a free energy of the ~~ligand~~ conformation in the protein; and

(ii) subtracting a sum of a [[the]] free energy of the protein and [[the]] a free energy of the ~~ligand~~ conformation from [[the]] a free energy of the ~~ligand~~ conformation in the protein~~; and~~

~~selecting for each ligand in the set of ligands the lowest calculated binding energy in the optimized preferred binding conformations, and~~

~~outputting the selected calculated binding energies as the predicted binding energies for the predicted binding conformations of the set of ligands, wherein the method steps are performed by a programmable processor executing a program of instructions~~.

47. (Currently amended) [[A]] The computer program product of claim 31 ~~on a computer-readable medium for modeling ligand-protein binding interactions~~, the computer program product further comprising instructions operable to cause a programmable processor to:

~~provide structural information describing the structure of a protein and each ligand in a set of one or more ligands;~~

~~use the structural information for the protein to identify a binding region of the protein;~~

~~identify a plurality of preferred binding conformations for each ligand in the set of ligands in the binding region, the preferred binding conformations being determined by generating a set of configurations for each ligand by applying a coarse-grained docking algorithm and ranking initial conformations for each ligand in the set of ligands at the binding region using energy scoring;~~

~~optimize the preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects;~~

calculate a binding energy for each ~~ligand in~~ conformation of the preferred set of ~~ligands~~ conformations ~~in the corresponding optimized preferred binding conformations, the binding energy being calculated~~ according to a scoring function selected from the group consisting of:

(i) subtracting a [[the]] free energy of the ~~ligand~~ conformation in water from [[the]] a free energy of the ~~ligand~~ conformation in the protein; and

(ii) subtracting a sum of a [[the]] free energy of the protein and [[the]] a free energy of the ~~ligand~~ conformation from [[the]] a free energy of the ~~ligand~~ conformation in the protein~~; and~~

~~select for each ligand in the set of ligands the lowest calculated binding energy in the optimized preferred binding conformations,; and~~

~~output the selected calculated binding energies as the predicted binding energies for the predicted binding conformations of the set of ligands~~.

48. (New) A system for identifying one or more ligand conformations that bind to a protein, the system comprising:

a memory; and

a processor, wherein the processor is configured to execute instructions operable to:

obtain structural information for the protein and for one or more ligands;
identify at least one binding region of the protein;
apply a coarse-grained docking algorithm to identify a plurality of binding conformations for the one or more ligands in the binding region;
select best conformations from the binding conformations for the one or more ligands;
optimize the best conformations using molecular mechanics;
using annealing molecular dynamics including solvation effects to further optimize a subset of the best conformations;
minimize a preferred set of conformations from the subset of the best conformations using molecular mechanics;
calculate a binding energy for each conformation of the preferred set of conformations;
rank the conformations of the preferred set of conformations based on the calculated binding energies;
select for each of the one or more ligands the conformation of the preferred set of conformations having the lowest calculated binding energy; and
output a data file comprising a list of selected ligand-protein conformations having the lowest calculated binding energy, and their respective binding energies.

49. (New) The system of claim 48, wherein the processor is further configured to execute instructions for calculating the binding energy according to a scoring function selected from the group consisting of:

(i) subtracting the free energy of the conformation in water from the energy of the conformation in the protein; and

(ii) subtracting a sum of the free energy of the protein and the a free energy of the conformation from the a free energy of the conformation in the protein.

50. (New) The method of claim 1, wherein the annealing molecular dynamics uses an all atom forcefield selected from the group consisting of: AMBER, CHARMM, DREIDING, MMFF, and MM3.

51. (New) The computer program product of claim 31, wherein the annealing molecular dynamics uses an all atom forcefield selected from the group consisting of: AMBER, CHARMM, DREIDING, MMFF, and MM3.

52. (New) The system of claim 49, wherein the annealing molecular dynamics uses an all atom forcefield selected from the group consisting of: AMBER, CHARMM, DREIDING, MMFF, and MM3.

53. (New) The method of claim 1, wherein the coarse-grained docking algorithm is a Monte Carlo algorithm.

54. (New) The computer program product of claim 31, wherein the coarse-grained docking algorithm is a Monte Carlo algorithm.

55. (New) The system of claim 49, wherein the coarse-grained docking algorithm is a Monte Carlo algorithm.